Timing of Initial Antibiotic Treatment for Febrile Neutropenia in the Emergency Department: The Need for Evidence-Based Guidelines

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Abstract

Guidelines for the treatment of febrile neutropenia (FN) universally recommend the prompt initiation (<60 minutes) of antibiotic therapy for patients with this complication presenting to medical settings. Unfortunately, administration delays exist in emergency departments where patients with FN frequently seek care. Future guidelines should be based on investigations that clearly indicate the effectiveness of rapid antibiotic therapy. If definitive investigations identify an optimal time period for the initial administration of antibiotics for patients with FN, administrative efforts will be developed to improve the emergency department care of these critically ill patients with cancer. (*J Natl Compr Canc Netw* 2014;12:1569–1573)

Over the past several decades, the development of effective chemotherapeutic regimens has significantly improved the overall survival of patients with cancer.^{1–4} Unfortunately, many of these treatment regimens cause profound bone marrow suppression with resultant leukopenia that renders these patients susceptible to serious infections, often with fever as the only clinical finding.^{5–8} This complication, known as *febrile neutropenia* (FN), occurs in 10% to

30% of patients undergoing chemotherapy (depending on several factors) and causes significant morbidity and mortality, with important long-term implications regarding the use of health care resources.^{9–14} A recent national study of patients with FN treated at 115 medical centers throughout the United States estimated an in-hospital mortality rate of 9.5% with a mean hospital stay of 11.5 days.¹⁵

The modern management of FN began approximately 50 years ago when several landmark studies reported superior mortality and morbidity outcomes associated with empirical treatment with broad-spectrum antibiotics before the isolation of bacterial organisms.^{5,16–19} Since then, extensive clinical and research efforts have focused on developing the most effective antibiotic treatment regimens for patients with FN based on individual risk stratification and identification of the causative infectious organism.^{20–22} These efforts have also prompted the development of guidelines by various national and international organizations to maximize the treatment of chemotherapy-induced FN in adult patients across institutions and countries (Table 1).^{22–30} A universally accepted feature of empiric treatment is the prompt initiation of antibiotic therapy at the earliest possible time (within 30–60 minutes) in patients presenting with FN to a medical setting.

Because rapid assessment and initial antibiotic treatment of FN are considered critical, patients with cancer who have this complication are frequently evaluated and managed in the emergency department (ED) before hospitalization.^{31–38} However, despite recommendations for rapid initial antibiotic treatment of patients with FN, significant delays in administration still occur in this setting.^{32–39} Table 2 presents several studies that illustrate the delayed times to initial antibiotic treatment for adults with FN in EDs

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Table 1 Current Guidelines for Timing of Initial Antibiotic Treatment of Adult Patients With Febrile Neutropenia

Reference, Organization, and Region	Recommended Timing of Initial Antibiotic Treatment
Tam et al, ²² 2011 Victorian Integrated Cancer Services (Australia)	First dose antibiotic: within 30 minutes if systemically compromised; 1 hour if clinically stable
Freifeld et al, ²³ 2011 Infectious Disease Society of America (North America)	All patients who present with fever and neutropenia should be treated swiftly and broadly with antibiotics to treat gram-positive and gram-negative pathogens
Przybylo et al, ²⁴ 2011 United Kingdom Department of Health (United Kingdom)	Department of Health guidance mandates administration of intravenous broad-spectrum antibiotics within 1 hour
National Chemotherapy Advisory Group, ²⁵ 2009 (United Kingdom)	All hospitals which might receive patients with acute complications of cancer should ensure delivery of antibiotics occurs within 1 hour for patients presenting with neutropenic sepsis
Clinical Oncology Information Network, ²⁶ 2008 Royal College of Radiologists (United Kingdom)	Intravenous antibiotics should be started within 30 minutes in 100% of patients who have received recent chemotherapy and who are shocked
Marti et al, ²⁷ 2009 ESMO Guidelines Working Group (Europe)	Standard management of febrile neutropenia involves prompt administration of empiric broad-spectrum, intravenous antibacterial therapy with additional supportive care (eg, intravenous fluid, oxygen) as indicated
Penack et al, ²⁸ 2011 German Society of Hematology and Oncology (Germany)	Empirical antimicrobial treatment using broad-spectrum antibiotics must be started immediately in patients with neutropenia with sepsis
Flowers et al, ²⁹ 2013 ASCO (USA)	Patients with febrile neutropenia should receive initial doses of empirical antibacterial therapy within an hour of triage
Baden et al ³⁰ 2013 National Comprehensive Cancer Network (USA)	All patients with neutropenia should be treated empirically with broad-spectrum antibiotics promptly at the first sign of infection (ie, fever)

worldwide, indicating poor compliance with the recommendations noted in Table 1. In fact, the mean or median time to initial antibiotics ranged from 102 to 300 minutes, far exceeding the commonly recommend time of less than 60 minutes. Even for patients with severe sepsis or septic shock, a French multicenter study found that only 19 of 89 study subjects (21%) received initial antibiotic treatment within 90 minutes of their presentation.³⁶

It is generally accepted that early versus delayed antibiotic treatment in the ED is beneficial for patients with severe bacterial infections. In fact, several studies have demonstrated improved outcomes with earlier ED antibiotic treatment for sepsis, meningitis, and pneumonia.^{40–51} In particular, Kumar et al⁴¹ found that for patients in septic shock, “time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome.” An important consequence of these studies has been the development of guidelines that have reduced the time to initial antibiotic treatment for patients with severe infections in the ED setting.^{52,53} Unfortunately, findings from these

studies do not appear to have translated to faster initial antibiotic treatment for adult patients with FN in the ED setting.

Although it seems intuitive that all patients with FN should receive their initial antibiotic treatment within 60 minutes of presentation to an ED, this goal is problematic for several clinical and administrative reasons. For example, patients must be properly evaluated with laboratory tests and radiographs to determine neutropenia and identify a possible source of infection.⁵⁴ Unfortunately, broad-spectrum antibiotic administration is not without risk, and inappropriate initial empirical therapy has been associated with increased mortality and morbidity in certain patients with sepsis.^{55–58} Consequently, physicians are often reluctant to initiate empirical antibiotic treatment before confirming the diagnosis of neutropenia. In addition, because of the demand for emergency nurses and physicians to provide rapid care to many patients with different critical conditions, any administrative strategy aimed at reducing time to initial antibiotic treatment must be supported by

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Table 2 Times to Initial Antibiotic Treatment for Adult Febrile Neutropenia in ED Settings

Study and Setting	Definition of Febrile Neutropenia	ED Patient Visits	Mean ANC	Demographic Distribution	Received Antibiotics in the ED	Overall Mortality	Time to Initial Antibiotic Treatment
Perrone et al, ³² 2004 Hospital of the University of Pennsylvania (USA)	Chemotherapy Temp >100.4°F ANC <1000/mm ³	55	436/mm ³	Mean age, 52.0 y with 53% men	55/55 (100%)	2/55 (3.6%)	170 min (mean)
Nirenberg et al, ³³ 2004 New York - Presbyterian Hospital/Columbia University (USA)	Chemotherapy or radiation therapy Temp >100.9°F ANC <1000/mm ³	23	400/mm ³	Mean age, 56.0 y with 53% men	23/23 (100%)	0/23 (0%)	210 min (median)
Courtney et al, ³⁴ 2007 Northwestern Memorial Hospital (USA)	Temp ≥100.4°F ANC ≤500/mm ³	57	93/mm ³	Mean age, 58.0 y with 52% men	52/57 (91%)	6/57 (10.5%)	102 min (median)
Lim et al, ³⁵ 2012 University of Alberta Hospital (Canada)	Temp >100.4°F WBC <1000/mm ³ or ANC <500/mm ³	128	100/mm ³	Median age, 51.0 y with 54% men	NA	NA	234 min (median)
Lim et al, ³⁵ 2012 Royal Alexandra Hospital, Grey Nuns Community Hospital, and Misericordia Community Hospital (Canada)	Temp >100.4°F WBC <1000/mm ³ or ANC <500/mm ³	73	100/mm ³	Median age, 57.0 y with 62% men	NA	NA	294 min (median)
Andre et al, ³⁶ 2010 47 French hospitals (France)	Temp >100.4°F WBC <1000/mm ³ or ANC <500/mm ³	198 (89 with sepsis or shock)	NA	Mean age, 61.0 y with 61% men	NA	NA	<90 min in 19/89 (21%) patients with sepsis or shock received antibiotics
Swajcer et al, ³⁷ 2011 Six hospitals of the Winnipeg Regional Health Authority (Canada)	Chemotherapy Temp >100.4°F ANC <1500/mm ³	68	230/mm ³ (median)	Median age, 59.5 y with 45% men	NA	6/68 (8.8%)	300 min (median)
Sammur et al, ³⁸ 2012 Addenbrooke's hospital (UK)	Chemotherapy Temp >100.4°F ANC <1000/mm ³	10	NA	NA	NA	NA	154 min (median)
Perron et al, ³⁹ 2014 Royal University Hospital, University of Saskatchewan (Canada)	Chemotherapy, Temp >100.4°F ANC <500/mm ³	105	210/mm ³	Median age, 60.0 y with 41% men	NA	4/105 (3.8%)	150 min (median)

Abbreviations: ANC, absolute neutrophil count; ED, emergency department; NA, not available; temp, temperature.

convincing evidence of a positive clinical effect before it will be integrated into the care of patients.^{59,60}

The authors believe that future guidelines and protocols recommending the rapid (<60 minutes) initiation of antibiotic treatment for FN should be based on adequately powered and valid investigations that clearly indicate the effectiveness of this intervention. Only a few small studies have attempted to measure the effect of timing of initial antibiotic treatment in adult

patients with neutropenia. Swajcer et al³⁷ found no effect of antibiotic timing on 30-day mortality or length of hospital stay, but used only univariate analysis of 68 patients (with 6 deaths) and did not adjust for severity of illness or other potentially confounding factors to provide a valid measure of effect. Sammur and Mazhar³⁸ assessed the effects of antibiotic timing using 22 oncology ward and 10 ED patients, and found a strong correlation between the door-to-antibiotic interval and inpatient

length of stay ($R=0.84$), and that patients received their initial dose of antibiotics faster when they presented to an oncology ward rather than the ED. Lynn et al⁶¹ found earlier administration of antibiotics to be associated with fewer serious complications (eg, unstable hemodynamic status, respiratory distress, altered mental status, newly developed arrhythmia, death) during hospitalization in a study of 78 patients with 81 episodes of FN presenting to the ED. And finally, Perron et al³⁹ found delayed antibiotic administration to be associated with longer lengths of hospital stay but not mortality. Unfortunately, these studies were significantly underpowered and provided conflicting evidence of the effects of the timing of initial antibiotic treatment for adult patients presenting to the ED with FN. As a result, no evidence-based recommendations exist for the timing of ED antibiotic management of adult patients with FN.

Of particular note, in a recent study of 653 pediatric patients, Fletcher et al⁶² investigated the effects of time to antibiotic administration on FN in 3 patient care areas: the inpatient setting, ED, and outpatient clinical setting.⁶² The study included 1628 episodes of FN over an 8-year period and found that the delayed administration of initial empiric antibiotics was associated with a composite adverse event outcome score that included mortality, pediatric intensive care unit admission, and the need for intravenous fluid resuscitation. This study also found that the median time to antibiotics was 145 minutes in the ED versus 93 minutes in the outpatient clinical setting. In addition, the risk for an adverse event was 15.7% among pediatric patients with FN in the ED versus 6.5% among those in the outpatient clinical setting. Although these findings may not be directly generalizable to adult patients because of pathophysiologic differences between adults and children regarding sepsis,⁶³ they provide additional information emphasizing the need for improved care of patients with cancer in ED settings.

The authors believe that larger and more definitive clinical investigations should be conducted to identify an optimal period for the initial administration of empiric antibiotics in adult patients with FN. If beneficial outcomes of earlier initial antibiotic treatment are illustrated, new administrative efforts will likely be developed to improve the ED care of patients with this severe, cancer-related complication. Several small studies in different clinical settings have already indicated that administrative interventions can substantially reduce initial time to antibiotic treatment for pediatric and adult patients

with FN.⁶⁴⁻⁶⁷ Effects of early versus delayed antibiotic treatment in various subgroups of patients with FN (based on demographic, clinical characteristics, type of underlying malignancy, degree of immune suppression, and prior allogeneic stem cell transplant) should also be estimated to address heterogeneous risks for death. In addition, future translational research should include assessments of administrative interventions aimed at reducing the time to initial empiric antibiotic treatment of FN in the ED setting, with decision-analytic studies to assess the cost-effectiveness of providing early versus delayed initial antibiotic treatment.

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